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Review Article

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Serotonin and Tryptophan Depletion in Anorexia Nervosa

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ABSTRACT

Anorexia nervosa is characterized by a variety of symptoms, including restricting food, low body weight, and a fear of gaining weight. It also has the highest mortality rate of neuropsychiatric disorders, affecting approximately 4% of females and 0.3% of men. While the neural mechanisms of eating disorders are not as precise as for other psychiatric disorders, emerging approaches to better comprehend the neurobiology of eating disorders have focused on the identification of the differences relating to the presence and metabolism of both dopamine and serotonin. It's suggested that those who are malnourished encounter a decrease in serotonergic tone, which is measured by a decrease in the serotonin metabolite 5-hydroxyindolacetic acid in the cerebrospinal fluid, dulled plasma prolactin response to serotonin agonists, as well as a reduction in the binding of platelets imipramine and paroxetine. A theory is that the decrease in the influx of tryptophan leads to a reduction of central nervous serotonin, which then imitates the effects of the restriction of food within the brain's serotonin system.

Introduction

Anorexia nervosa is a mental health condition that has numerous associated symptoms. These symptoms can include self-starvation, heightened anxiety, and amenorrhea as identified. Alberts, Owe-Larsson, & Urbanska, [1]. Whereas Yokokura, et al, reported the symptoms of constant restriction of energy, low body weight that is significant, and fear of gaining weight were identified [2]. Additionally, Weinert, et. al., suggested that those with anorexia nervosa may be obsessional, perfectionistic, and engage in harm avoidance [3]. Of the mortality rates of neuropsychiatric disorders, anorexia nervosa has the highest affecting approximately 4% of females and 0.3% of males globally, and the prevalence of anorexia nervosa in those under 15 has increased [1]. Anorexia nervosa typically peaks in prevalence between the ages of 14 and 17, and despite research, there are no specific pharmacological interventions that lead to a decrease in the mortality rate of anorexia nervosa that lessens the damaging medical consequences [3].

Data collected from 2013 to 2022 suggested that 5.5-17.0% of young women and 0.6-2.4% of young men have met the diagnostic criteria for an eating disorder per The Diagnostic and Statistical Manual of Mental Disorders (DSM) by the time they reach early adulthood [1]. Anorexia nervosa was also reported in women at 0.8-6.3% and 0.1-0.3% in men who are considered especially high risk and of sexual and gender minorities.

The Manifestation of Anorexia Nervosa

It is suggested that women are more vulnerable to restricting food, which can be due to a tryptophan level that is chronically deficient as well as being insufficient in bioavailability [4]. Moreover, it has been proposed that the behaviors associated with undernourishment are not primary, and alterations in the brain's serotonin system can lead to decreased regulation related to impulse control, appetite, or mood linked to anorexia nervosa. The manifestation of anorexia nervosa comes before the disruption of neuronal serotonin change, leading to preceding symptoms including inhibition, anxiety, and obsessionality [4]. Since tryptophan is the predecessor of serotonin, a depletion can change the neurotransmission of serotonin, and it has been revealed that there is a reduction in plasma of the tryptophan/large neutral amino acid ratio and tryptophan levels in those who are underweight.

While the neural mechanisms of eating disorders are not as clear as for other psychiatric disorders, emerging approaches to better

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comprehend the neurobiology of eating disorders have focused on the identification of the differences relating to the presence and metabolism of both dopamine and serotonin [5]. Through advances in neuroimaging and neuroscience, it is becoming progressively more possible to identify how human behavior is governed, including connecting brain activity to maladaptive behaviors. The etiology of anorexia nervosa is seen as complex and it contains congenital and environmental factors [1]. Typically, those with anorexia nervosa also present with major depressive disorder, an anxiety disorder, or other psychiatric comorbidities. Behavioral dysfunctions associated with anorexia nervosa include impaired appetite, distorted impulsive control, neuroticism, anxiety, and lowered mood [1].

While someone with anorexia nervosa can suppress the desire to eat despite being undernourished, when other rewards are presented, like sex or pleasant touch, they can also display anhedonic responses to those rewards. Within the brain the ventral striatum is a region associated with the reward system, and in that region there have been altered neural responses to disorder-related stimuli like food, as well as disorder-unrelated stimuli like money identified [6]. There has been a growing amount of information looking at the role of serotonin in reward processing versus looking at dopamine, which has been assumed to be the main neurotransmitter involved in reward processing. In fact, serotonin can either increase or inhibit the effect dopamine has on the brain's reward system [6].

Serotonin has effects on impulse control, obsessions, mood, and appetite, and for those with anorexia nervosa, it has been found that there is a dysfunction in the serotonergic system [7] Additionally, in those with anorexia nervosa, dysphoric moods can be due to the upregulating of the serotonergic system that is triggered by chronic stress. When an individual diets, there is a decrease in the levels of serotonin as well as dysphoric moods; this can then perpetuate a serotonergic-homeostatic stress and starvation cycle that also raises cortisol and neuroinflammation [7].

Serotonin, Anorexia Nervosa, and the Reward System

Reward value was assessed by Boehm, et. al, discussing the salience network and how it plays a vital role in the ability to detect, filter, and integrate biologically important salient stimuli which do incorporate the homeostatic regulation and reward value [8]. When there are insufficiencies in salience findings, this can lead to various consequences, including issues with the higher-order cognitive functioning as well as being linked to various mental disorders [8]. Anorexia nervosa can lead to alterations within the salience network, specifically in the insular cortex, which has displayed an altered resting state functional connectivity. Additionally, serotonin variations are connected to resting state functional connectivity within the salience network in those with anorexia nervosa and eating disorder pathology [8].

Regions of the brain, including the insula, visual cortex, and the somatosensory cortex, which also includes the supramarginal gyrus, send projections to the orbitofrontal cortex, and these regions are thought to play a crucial role in interpreting the affective value of reward as well as punishment that correlated to the senses [8]. Furthermore, when the reward value of stimuli is exemplified, the orbitofrontal cortex is a part of the representation of emotions, and it can be deduced that emotions generate rewards as well as to adverse stimuli. Steding et. al, heavily focused on the reward system as it related to anorexia nervosa and found that the reward system is regulated by serotonin [6].

Serotonin, Tryptophan, and Anorexia Nervosa

While data is inconsistent, there may be a reduction in white and gray matter, and brain atrophy can be observed via morphological assessments. Furthermore, disturbed functioning may be demonstrated through past clinical data [1]. Increased serotonin availability heightens the risk of anorexia nervosa, and focusing on serotonin may possibly be an encouraging neurobiological model [6]. Serotonin is also associated with mood regulation, anxiety, and the modulation of appetite, which is thought crucial in the etiology of anorexia nervosa [8].

The serotonin system is comprised of 14 or more receptor subtypes; among those the 5HT1A subtype plays the part of autoreceptor on the raphe nucleus creating serotonin as well as postsynaptic receptors within in many regions of the brain stimulating serotonergic estimates [2]. The 5HT1B subtype is responsible for inhibiting the release of neurotransmitters on the serotonergic and nonserotonergic presynaptic receptors. In anorexia nervosa, the 5HT1A receptor is increased unrelated to whether they are underweight or post-recovery [2]. Likewise, the 5HT2A receptor decreased in those who recovered from anorexia nervosa but not those who were underweight. Due to the identification of the reduction of 5HT2A in those with anorexia nervosa, it can be concluded that the pathophysiology of anorexia nervosa lies in the serotonin system [2].

It has been proposed that those who are acutely underweight are associated with a reduction of serotonergic tone, which is observed through a reduced level of the serotonin metabolite 5-hydroxyindolacetic acid in cerebrospinal fluid and a reduction in the platelet imipramine and paroxetine binding [8]. Additionally, a lower receptor binding capacity in the central nervous system and serotonin receptor density in the periphery has been observed in those with anorexia nervosa. An increase in serotonin availability may lead to anxiety which may be decreased when tryptophan is decreased [8]. Additionally, an increase in the serotonin subtype 5HT1A, in those with anorexia nervosa and post recovery from anorexia nervosa, tryptophan depletion led to an anxiolytic effect because of malnutrition [2].

It has been theorized that after recovery from anorexia nervosa, individuals enter a hyperserotonergic state as indicated by an increase in the availability of serotonin in the central nervous system [6]. The availability of tryptophan can decrease during the acute illness phase due to restrictive eating. Therefore, serotonin availability can decrease in the central nervous system leading to a hyposerotonergic state [6]. An individual can enter a hyperserotonergic state after being weight restored in those who have recovered from anorexia nervosa, which is designated by decreased blood platelet monoamine oxidase-B activity, an increase in serotonin content, alterations in central nervous serotonin and serotonin, and serotonin receptor binding capacity, and the elevation of 5-hydroxyindolacetic acid in the cerebrospinal fluid [8].

The Neuroscience of Tryptophan

Tryptophan and large neutral amino acids both fight to the transmitter that allows for amino acids to cross the blood brain barrier [1]. The quantity of tryptophan that passes into the brain is denoted by the peripheral tryptophan and large neutral amino acid ratio. Therefore, a peripheral parameter is measured that indicates the amount of tryptophan that is available in the brain [1]. Serotonin-transported protein is primarily found in the midbrain, brain stem, thalamus, and basal ganglia, and its role is to aid in the regulation of extracellular serotonin via reuptake [2]. In individuals with anorexia nervosa both higher and lower amounts of tryptophan have been found which is puzzling [1].

It is important to note that the bulk of serum tryptophan is altered along the kynurenine pathways into numerous neuroactive products designated as kynurenines [1]. Additionally, there is collected proof that the bilateral interactions of tryptophan metabolism along the kynurenine pathway and the inflammatory pathways are important. It has been suggested that glial cells are responsible for generating most kynurenines in the brain as well as anorexia nervosa pathophysiology [1]. Anorexia nervosa may be able to be defined as a disorder in which there is a reduction of dietary tryptophan that lessens serotonin synthesis as well as hinders kynurenine synthesis.

With anorexia nervosa, those individuals who are in the acute phase, meaning those who are currently underweight, have fewer serotonin metabolites within their cerebrospinal fluid compared to healthy control individuals [7]. Tryptophan is derived from food, and the starvation/dieting cycle present with anorexia nervosa can account for the lower serotonin metabolism. Starvation can cause tryptophan to become depleted, which then leads to the brain to increase the amount of serotonin receptors so the brain can more effectively use the serotonin [7].

Differentiation of Anorexia Nervosa Subtypes

There are two identified subtypes of anorexia nervosa: binge-eating/purging subtype in which an individual either engages in binging and purging or restricting without binging or purging [2]. Individuals with the binge-purge subtype of anorexia nervosa were reported to have lower levels of serotonin transporters availability within the anteroventral striatum and dorsal raphe in recovery than those with the restrictive subtype. Individuals with the restrictive subtype of anorexia nervosa differ from the binge/purge subtype in their clinical presentation, impulsivity, neurocognitive functioning, emotion regulation and self-regulatory behavior, and brain activation [9]. Furthermore, the two subtypes of anorexia nervosa differences were related not just to anthropometric characteristics but variations in body weight throughout the course of the disorder as well.

For those in the refeeding phase of anorexia nervosa, tryptophan/large neutral amino acid ratio is increased and is correlated with a reduction in symptoms of depression [4]. Improvement of serotonin release in the brain can impact the regulation of appetite and meal consumption based on the extent of carbohydrates and protein in the meal. There is an encouraging connection between anxiety, depression, and serotonin total blood levels [4]. Behaviors associated with dietary restrictions may lead to the reduction of cerebral serotonin synthesis as well as a decrease in serotonin concentrations. This decrease in serotonin concentration is within the hypothalamic which causes hyperactivity that strengthens weight loss behaviors [4].

The Effects of Tryptophan Depletion on Anorexia Nervosa

It has been proposed that those who are malnourished encounter a decrease in serotonergic tone which is measured by a decrease in the serotonin metabolite 5-hydroxyindolacetic acid in the cerebrospinal fluid, dulled plasma prolactin response to serotonin agonists, as well as a reduction in the binding of platelets imipramine and paroxetine [8]. It has also been described that in the central nervous system there is a reduction in serotonin receptor density within the periphery. Cognitive alterations have been indicated because of tryptophan depletion, as the neural functions in the brain that are connected to affective or cognitive functioning are controlled by the depletion of acute tryptophan [8]. For example, the amygdala is used in emotional processing and the prefrontal areas are used in executive functioning.

Acute tryptophan depletion briefly quells the amount of tryptophan that crosses the blood-brain barrier, which can be induced by the ingestion of a tryptophan-free amino acid drink, of a well-defined ratio, that also is comprised of large neutral amino acids [3]. It has been theorized that the decrease in the influx of tryptophan leads to a reduction of central nervous serotonin, which then imitates the effects of the restriction of food within the brain's serotonin system. Additionally, serotonin in the central nervous system is reduced, which may lead to the individual going into a hyposerotonergic state [6]. Individuals with anorexia nervosa, who are underweight, display a decrease in tryptophan plasma levels in addition to a decrease in the concentration of 5-HIAA in cerebral spinal fluid, a decrease in platelet imipramine and paroxetine binding, serotonin 2a receptors have a lower density in the peripheral, and there is a reduction in central nervous serotonin HT2a receptor binding.

Individuals with anorexia nervosa enter a homeostatic cycle caused by the reduction of tryptophan, and by reducing the consumption of food which leads to the individual feeling better [7]. Serotonin levels will begin to rise when the individual eats foods containing tryptophan, which will then trigger intense anxiety and emotional turmoil. Additionally, serotonin depletion within the acute phase of anorexia nervosa may be able to account for the body image issues that are typically associated with the disorder [7].

Why are Serotonin and Tryptophan Important

Serotonin holds essential functions related to appetite regulation, and in individuals who are acutely ill display a decrease in tryptophan plasma concentrations as well as a diminished concentration of 5-hydroyindoleacetic acid within the cerebrospinal fluid and in the peripheral blood plasma [3]. Tryptophan depletion is intensified by stress, and peripheral and central nervous serotonin levels decrease because of inflammation [1]. While an individual may utilize starvation to reduce dysphoria, the depletion of serotoninergic transmission can lead to a depressed mood, which can then exasperate the course of anorexia nervosa. Conversely, increased levels of tryptophan were associated with a decrease in symptoms of depression for those in the refeeding stage [1].

Tryptophan depletion may lead to an anxiolytic effect, which may lead those with anorexia nervosa to restrict energy intake,

and subsequently, a tryptophan decrease that is dietary induced [2]. It has been hypothesized that food restrictions related to anorexia nervosa alleviate a hyperserotonergic state, and that acute tryptophan depletion may have the ability to normalize this hyperserotonergic functioning in those recovered from anorexia nervosa [6]. Furthermore, acute tryptophan depletion may indicate the stabilization of the functional connectivity involving the salience network and the orbitofrontal cortex in those recovered from anorexia nervosa [8]. It is this that provides additional backing to the hypothesis that those with anorexia nervosa may be predisposed to a hyperserotonergic state.

Tryptophan is an important element of diet as it performs a vital function in protein synthesis, which is a precursor for serotonin [4]. Tryptophan is also accountable for the regulation of caloric intake, and a decrease in tryptophan may lead to the restriction of food, specifically in females. Since tryptophan is the precursor for serotonin, a deficit in tryptophan may lead to a drastic alteration in serotoninergic neurotransmission [4]. Tryptophan depletion is also present in reward pathways and is thought to be altered in those with anorexia nervosa [6]. Furthermore, tryptophan depletion has been studied to assess the pliability of cognitive functions like that seen in reward [6].

Tryptophan and Animal Models

The role of tryptophan was in controlling food intake using animal models looking at the correlation between tryptophan and brain serotonin [1]. Animals were provided with low protein high carbohydrate food, or they were injected with insulin. In these animals, levels of plasma and brain tryptophan did increase and were also associated with a brief increase in serotonin [1]. Alberts, Owe-Larsson, & Urbanska, reported that no change occurred in brain levels of tryptophan or serotonin when there was a larger increase of plasma tryptophan that was produced by the animal intaking protein-containing diets [1]. They additionally noted that plasma amino patterns would alter tryptophan uptake into the brain. This was done via competition between tryptophan and other large neutral amino acids [1].

Alberts, Owe-Larsson, & Urbanska, utilized rats and noticed that their food intake drastically decreased after an acute interleukin-1(IL-1) injection as well as noticed an increase of plasma large neutral amino acids and a reduction in plasma-free tryptophan [1]. A decrease in brain tryptophan and serotonin was also seen in the rats during a period of extended starvation. In rats who were subjected to starvation, hypothalamic tryptophan was decreased in rats who were starved, and starved and then refed, plasma tryptophan was decreased in those who were starved and those who were starved then refed rats, and serotonin was also shown to be reduced in rats who were starved, and those who were starved and then refed [1]. Serotonin was also shown to be reduced in some regions of the brain due to food restriction, but only in the male rats.

Critical Review

Boehm et. al., conducted a study in which they explored the hypothesis of individuals who have a predisposition for anorexia nervosa, or those who have recovered, undergoing a hyperserotonergic state [8]. This state is linked to anxiety that may be alleviated by the restriction of food because of the effect the reduced tryptophan precursor levels have on the availability of serotonin [8]. This study included data on 44 female participants, 22 who recovered from anorexia nervosa (containing 18 with the restrictive subtype and 4 with the binge-purge subtype), and 22 control participants who were all European descent. For this study, "recovered" was defined as meeting the diagnostic criteria for anorexia nervosa prior to the study, currently at a body mass index that is greater than 18.5 kg/m2 or in the 10th percentile or above if the participant is younger than 18.

The authors also analyzed seven seed regions including the salience network, the anterior cingulate cortex, the left and right anterior insula, the left and right rostral prefrontal cortex, and the left and right supramarginal gyrus [8]. Seed-based connectivity maps were run in the form of Fisher-transformed bivariate correlation coefficients. Individual and condition specific computations were completed looking at the blood-oxygen-level-dependent time series relating to each seed region, as well as addressing the individual voxel time series in the brain [8]. The results of this study did not find any differences that were significant between the test group and the control group in age, body mass index, and depression scores [8]. However, those who had recovered from anorexia nervosa displayed some lingering symptoms of the disorder.

Compared to the healthy control group, the test group displayed a considerable decrease in tryptophan levels [8]. Looking at the results of acute tryptophan depletion related to the control group, there was a significant difference relating to the resting-state functional connectivity involving the right orbitofrontal cortex extending to the frontal pole. Analyzing the resting-state functional connectivity noted a main effect that had increased for the group condition between the salience network seeds and the prefrontal regions like the inferior and medial frontal cortex, which can be associated with a higher level of cognitive control [8]. There was also a significant main effect between the salience network and the thalamus, leading to a raised resting state of functional connectivity.

Furthermore, those who had recovered from anorexia nervosa displayed an elevation in connectivity in the depletion phase versus the control group [8]. The analysis of the resting-state functional connectivity values shown in interactions between the groups was motivated by the idea that individuals recovered from anorexia nervosa displayed higher connectivity in the depletion condition versus the healthy control condition. In the individuals within the healthy control group, their resting-state functional connectivity was decreased in the depletion condition [8]. In the healthy control condition, this connectivity was like that of the individuals who have recovered from anorexia nervosa within the depletion condition. Examining an exploratory correlation analysis, there was no significant relationship identified between the connectivity in the orbitofrontal cortex throughout both the depletion and healthy control phases of the study for any of the included clinical measures for those with anorexia nervosa who were recovered [8].

A study conducted by Weinert, et. al expressed that the etiology of anorexia nervosa lacks understanding; however, the serotonin system has been identified as possibly being able to aid in gaining an understanding of the neurobiological basis of anorexia nervosa [3]. The authors speak to the role that serotonin has in

anorexia nervosa and how serotonin is also linked to numerous symptoms and traits that are associated with those at a higher risk of developing anorexia nervosa [3]. These symptoms included heightened anxiety and low mood. It has been indicated that there are modifications in the central nervous serotonin system in those with anorexia nervosa who are acutely underweight, as well as those who are recovered, display decreased levels of tryptophan.

This study collected data from 49 female participants, 22 who had recovered from anorexia nervosa ages 17-26, and 27 age-matched health controls. Among the 22 recovered participants, 22 were diagnosed with the restrictive subtype and 2 with the binge/purge subtype. Like the Bohem study, to be considered recovered, an individual needs to have maintained a body mass index of >18.5 for those 18 and older for 12 months of the study, be menstruating, and have refrained from the eating disorder patterns associated with each diagnosis [3]. Participants in the healthy control group must be considered normal weight, meaning having a body mass index between 18.5 and 34.9kg, and be eumenorrheic. A psychiatric illness history excluded health control when reported in the semi-structured interview [3]. This included psychiatric diagnoses including bulimia nervosa, schizophrenia, substance use, bipolar disorder, and suicidality. Additionally, those with an IQ of lower than 85, had an organic brain syndrome, had a medical condition that could impact appetite, were pregnant, or were using psychotropic medication were also excluded from the study.

To calculate the depletion effect, the authors calculated the plasma tryptophan ratio to the large neutral amino acids specifically valine, methionine, isoleucine, leucine, phenylalanine, and tyrosine [3]. The tryptophan/large neutral amino acid ratio is said to be a reliable way to identify the distribution of tryptophan through the blood brain barrier and, therefore, the making of tryptophan. This study had the goal of gaining proof for or against the serotonin hypothesis of anorexia nervosa by aiming to recreate a prior outcome that suggested that a dietary induced tryptophan depletion would have anxiolytic effects in those who have recovered from anorexia nervosa. Results of the study identified a substantially significant relationship between the acute tryptophan depletion group and the control group pre- and post-procedure. This proved the wanted differential effect of both conditions on the tryptophan and large natural amino acid ratio [3].

Steding, et. al conducted a study in which they explored the serotonin hypothesis of anorexia nervosa which suggests that those who have a predisposition to anorexia nervosa, or those who have recovered, experience a central nervous hyperserotonergic state [6]. This state then leads to the reduction of the intake of food to decrease the available serotonin as well as lessen any adverse mood states. There is an encouraging neurobiological model for anorexia nervosa which is centered on serotonin [6]. Furthermore, the precursor for serotonin, tryptophan, can be a potential risk factor for the development of symptoms of depression.

This study was comprised of data from 47 female participants, 22 who had recovered from anorexia nervosa, and 25 healthy controls; all participants partook in both the acute tryptophan depletion and the healthy control depletion conditions [6]. Like the prior studies, to be deemed recovered, a participant had to have a body mass index of >18.5 or be over the 10th percentile for the participant's age. Additionally, participants must be menstruating and have refrained from any eating disorder patterns including binging or restricting over the last 12 months. For the healthy control group, participants must be considered "normal weight," be eumenorrheic, and have no psychiatric illness history [6].

The researchers utilized a double-blind, randomized crossover design in which participants were given a tryptophan depletion beverage after modifying meals to be low protein prior to the study. Moreover, the acute tryptophan depletion was used in conjunction with an instrumental motivation task that focused on monetary rewards through functional magnetic resonance imaging (fMRI) [6]. The aim of this instrumental motivation task was to investigate the serotonergic alterations of the reward-related neural responses surrounding anorexia nervosa. Steding et al., also hypothesized that a hyperserotonergic state is a foundational risk factor for the development of anorexia nervosa [6]. It is also hypothesized that this risk is momentarily decreased through the restriction of food at the start of the disorder; however, because of the severity of emaciation, it declines to the hyposerotonergic state at the acutely underweight state of anorexia nervosa [6]. Thus, an investigational decrease in serotonin through acute tryptophan depletion may "normalize" distorted brain reactions of serotonin in those who have recovered from anorexia nervosa.

A study conducted by Yokokura, et. al., looked at body image distortions associated with anorexia nervosa and how it may be influenced by anomalies in the serotonin system, specifically the serotonin transporter [2]. Additionally, the researchers utilized positron emission tomography (PET) scanning of underweight individuals with anorexia nervosa, which identified variations in serotonin receptors but not serotonin transporters [2]. This study had the goal of revealing the clinicpathophysiology of anorexia nervosa with attention to serotonin transporters and cognitive functioning.

This study included data from female participants only, as it was reported that women display a higher prevalence of anorexia nervosa. Participants must have an anorexia nervosa diagnosis based on the criteria per The DSM be between 18 and 35 years old. Participants were excluded if there was an existence of white matter changes on the T2 and fluid-attenuated inversion recovery (FLAIR) MRI images, if participants used medications including antipsychotics, antidepressants, anxiolytics, or hypnotics within the past 3 months, have a major medical illness, and have past occurrences of neurological or psychiatric disorders outside of anorexia nervosa [2].

Participants included 22 females with active anorexia nervosa, 23 with the restrictive subtype, 10 with the binge/purge subtype, and 20 age-matched females as a healthy control group. Due to past research, the researchers in this study chose to measure 17β-estradiol in participants as it was reported to be lower in those with anorexia nervosa [2]. So, the researchers here measured 17β-estradiol levels in all participants. 17β-estradiol has also been associated with affecting cognitive functioning in

women who are considered healthy and is considered the lowest during the follicular phase [2].

Results of this study show that the bonding potential (BPND) values of [11C]DASB were significantly lower in participants with anorexia nervosa and subtypes when compared to the healthy control group in the medial parietal cortex. Participants with anorexia nervosa also displayed a significantly lower bonding potential value within the dorsal midbrain, and there were no significant changes in BPND values of [11C]DASB in participants with the restrictive subtype and the binge/purge subtype of anorexia nervosa [2]. Results suggested that the availability of serotonin transporters in the medial parietal cortex in those with anorexia nervosa, compared to the healthy control group, was reduced.

A past PET study suggested normal serotonin transport levels within each of the subtypes of anorexia nervosa related to healthy control participants [2]. This indicates that serotonin transporter availability was reduced in underweight individuals with the restrictive subtype and normal in those who had recovered. Serotonin transport availability within the dorsal raphe in those recovered from the restrictive subtype was unaltered in those who were underweight, and a reduction in serotonin transport availability with the dorsal raphe may indicate a pathophysiological sign of preceding aspects or following the onset of anorexia nervosa [2]. This study suggested that serotonin transport availability did reduce in the parietal cortex in those with anorexia nervosa and the restrictive subtype and that it reduced in the parietal cortex as well as the dorsal raphe in those with the restrictive subtype [2].

Limitations

Anorexia nervosa is a disorder whose etiology is unknown, and this is a statement that is shared by many researchers [4]. Albers, Owe-Larsson, & Urbanska (2024) reported that data collected on anorexia nervosa relating to the depletion of tryptophan is limited and that what research there is, is not straightforward. The studies presented here all utilized smaller sample sizes, and Boehm et. al., noted that larger sample sizes would be required to verify the results. Weaknesses related to acute tryptophan depletion were explored despite being used extensively and validated for adolescents and adults [8].

One limitation reported by Boehm, et. al was that the impact of acute tryptophan depletion central nervous serotonin availability could only be determined by measuring the tryptophan/large neutral amino acid ratio [8]. However, in this study, the researchers were able to assess the efficacy of acute tryptophan depletion using PET, which could measure the flood of tryptophan into the brain. Another limitation noted was what the definition of what anorexia nervosa recovery was as the definitions are vast, this has led to an inability to accurately compare studies and their results [8]. Boehm, et. al., added that future research could gain benefits from utilizing longer length studies to increase the consistency of the resting-state-functional connectivity [8].

The Weinert, et. al., study identified noteworthy limitations [3]. This study used assessments that were self-reported for the purpose of assessing anxiety and mood. Substitutions in dependent measures were also used, for example, implicit measures, expert measures, and neuropsychological constraints [3]. Ethically, there were limitations on including underweight participants with anorexia nervosa for the fear that acute tryptophan depletion would lead to relapses or worsening of symptoms. This study did not include enough participants who recovered from either the restrictive subtype or the binge/purge subtype; therefore, there was a lack of significant results for this group [3]. Weinert, et. al., proposed the need for more thorough knowledge of the neurobiology of anorexia nervosa as well as the possibility of the serotonin hypothesis to further the path for the creation of necessary treatment options [3].

The Steding et. al., study identified several of their own limitations related to interpretation [6]. They noted that a within-subject design is more powerful than a between-subject design, and that this might be able to identify results in smaller sample sizes. However, they proposed that larger sample sizes in future research would be more beneficial to better duplicate and verify the presented results [6]. This study utilized monitory rewards, and while it allowed for an overview of reward processing, it may be likely to display varied results in those with anorexia nervosa. Therefore, subsequent studies should consider other sources of rewards that may be more revealing to the serotonin hypothesis [6].

Steding et. al., also mentioned that acute tryptophan depletion was extensively utilized with adolescents and adults, but interventions do have their weaknesses [6]. They also shared the limitation, matching Boehm, et. al., that the effect of acute tryptophan depletion on the brain's serotonin availability is assessed by the plasma tryptophan/large neutral amino acid ratio using more indirect instruments [6,8]. Therefore, assumptions made regarding selective serotonergic outcomes should be constructed with care.

Yokokura, et. al., discussed limitations as well as it relates to body image, serotonin transporters, and anorexia nervosa [2]. This study included participants with anorexia nervosa who also regularly smoked and used alcohol, but there are no significant impacts of smoking or drinking on [11C]DASB BPND. The results of this study identified significant variations in body mass index between the restrictive subtype and the binge/purge subtype of anorexia nervosa [2]. A cross-sectional study design was utilized, but a longitudinal study that included both subtypes may be more useful to explain the differences in serotonin vulnerability.

Eating Disorders in Males

a common limitation of the studies presented here was the use of only female participants. Future research would benefit from including male participants in studies researching anorexia nervosa. Yokokura, et. al., did reference a past study that identified lower serotonin transporter binding in the diencephalon, which related to reaction times that were longer in response to visual stimuli, which was associated with food in male participants who were considered healthy and lean [2]. However, their own study did not use male participants. The Weinert, et. al., study referenced males once, only mentioning the prevalence rate of anorexia nervosa between females and males [3].

Alberts, Owe-Larsson, & Urbanska referenced many studies that included male participants as this article was not a study itself

[1]. They spoke to the inclusion of male rats that were studied during periods of extended starvation, looking at hypothalamic tryptophan and serotonin levels. It was also articulated that outcomes regarding behavioral and biochemical limitations following the depletion of tryptophan in a variety of psychiatric disorders, for example, depression, bulimia nervosa, autism, and substance use, are also varying.

Rantala, Luoto, Krama, & Krams, spoke to males and "reverse anorexia" which is hypothesized function of the intrasexual competition that is associated with eating disorders and is something that specifically affects bodybuilders more than other men and boys [7]. Additionally, men who believe that they are too small physically despite being muscular express a more warped body image. Men were also included in data looking at individuals with obsessive-compulsive disorder (OCD) as obsessions with exercise, looks, and food are commonly associated with eating disorders [7]. It was reported, via a Swedish multigenerational family and twin study, that male participants had a 37-fold increased likelihood of having OCD while females had a likelihood that was 16-fold along with anorexia nervosa.

Future Direction of Research

The use of tryptophan as a supplemental therapy for anorexia nervosa can potentially be considered as a form of treatment but extensive studies are needed [1]. The research that is there on tryptophan and anorexia nervosa appears to strengthen the hypothesis that restricting the supply of tryptophan in those who are either predisposed to or recovered from anorexia nervosa and demonstrating undue transmission of serotonin can lead to the alleviation of dysphoric moods. In addition to tryptophan, central deficits of L-kynurenine supply and an impaired astrocytic making of kynurenic acid are also correlated to anorexia nervosa. Alberts, Owe-Larsson, & Urbanska suggested that amongst individuals with anorexia nervosa, when lower levels of L-kynurenine and kynurenic acid are revealed, aryl hydrocarbon receptors are weakened, which could have an impact on unusually lower body weight [1]. So, in addition to continuing research looking at the effects of tryptophan on anorexia nervosa, there is a need to research the effects of additional neurotransmitters and anorexia nervosa.

References

1. Alberts C, Owe-Larsson M, Urbanska EM. New perspective on anorexia nervosa: Tryptophan-Kynurenine pathway hypothesis. Nutrients. 2023 15: 1030.
2. Yokokura M, Terada T, Bunai T, Nakaizumi K, Kato Y, et al. Alterations in serotonin transporter and body image-related cognition in anorexia nervosa. NeuroImage Clinical. 2019. 23: 101928.
3. Weinert T, Bernardoni F, King J, Steding J, Boehm I, et al. No effects of acute tryptophan depletion on anxiety or mood in weight-recovered female patients with anorexia nervosa. European Archives of Psychiatry and Clinical Neuroscience. 2022. 273: 209-217.
4. Kałużna-Czaplińska J, Gątarek P, Chirumbolo S, Chartrand MS, Bjørklund G.How important is tryptophan in human health? Critical Reviews in Food Science and Nutrition. 2017. 59: 72-88.
5. Steinglass JE, Berner LA, Attia E. Cognitive Neuroscience of eating disorders. Psychiatric Clinics of North America. 2018. 42: 75-91.
6. Steding J, Ritschel F, Boehm I, Geisler D, King JA, et al. The effects of acute tryptophan depletion on instrumental reward learning in anorexia nervosa - an fMRI study. Psychological Medicine. 2022. 53: 3426-3436.
7. Rantala MJ, Luoto S, Krama T, Krams I. Eating Disorders: An Evolutionary Psychoneuroimmunological approach. Frontiers in Psychology. 2019. 10.
8. Boehm I, Hennig J, Ritschel F, Geisler D, King JA, et al. Acute tryptophan depletion balances altered resting-state functional connectivity of the salience network in female patients recovered from anorexia nervosa. Journal of Psychiatry and Neuroscience. 2022. 47: E351-E358.
9. Maïmoun L, Guillaume S, Lefebvre P, Bertet H, Seneque M, et al. Effects of the two types of anorexia nervosa (binge eating/purging and restrictive) on bone metabolism in female patients. 2018. Clinical Endocrinology, 88: 863-872.